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# **Antecedents of new-onset major depressive disorder in adolescence: a longitudinal familial high-risk study**

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Study concept and design: SC, GTH, FR, AKT, AT

Acquisition, analysis or interpretation of data: RBJ, SC, OE, GH, GTH, FR, AKT, AT, RS, FR, RS

Critical revision of the manuscript for important intellectual content SC, GH, GTH, FR, AKT, AT, RS, OE, RBJ, FR, RS

Statistical analysis: RS, GH, GTH, FR

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## **Abstract**

### **Importance**

Early onset major depressive disorder (MDD) is common in those at high familial-risk of depression and is associated with particularly poor long-term mental health, social and educational outcomes.

### **Objective**

To examine the developmental pathways that lead to first episode adolescent-onset MDD (incident cases) in those at high familial risk. We postulated a theoretically-informed model that enabled the simultaneous testing of different pathways to incident adolescent-onset MDD. These pathways were composed of contributions from familial/genetic and social risk factors as well as effects via specific clinical antecedents.

### **Design**

Four year longitudinal study of offspring of depressed parents.

### **Setting**

General community

### **Participants**

337 families where the index parent (315 mothers and 22 fathers) had experienced at least two episodes of MDD (recruited through primary care) and, at baseline, there was a biologically related child in the age range 9-17 years living with the index parent (197 girls and 140 boys, mean age = 12.4 years). Offspring with MDD prior to the study or at baseline (27), or with an episode of MDD that had remitted by follow-up (4) and missing baseline MDD data (2) were excluded. 92% of families completed the follow-up.

### **Main outcome measure**

Primary outcome: new-onset MDD; Secondary outcome: total DSM-IV MDD symptom score.

### **Results**

Fear/anxiety ( $\beta=.38$ ,  $p<.01$ ) and irritability ( $\beta=.12$ ,  $p<.05$ ) were significant independent antecedents of new adolescent-onset MDD but low mood ( $\beta= -.03$ ,  $p>.1$ ) and disruptive

behavior ( $\beta = -.08$ ,  $p > .1$ ) were not. Results were similar for DSM-IV symptom count at follow-up. All the measured familial/genetic and social risk indicators directly influenced risk for new-onset MDD rather than indirectly through acting on dimensional clinical antecedents.

### **Conclusions and relevance**

There are multiple pathways to first-onset adolescent depression in those at familial risk. Anxiety and irritability may be additional clinical phenomena to be included as targets in primary preventive interventions focusing on the child. As well as targeting clinical phenomena in parents and children, depression prevention methods in high-risk groups may need to take into consideration social risks such as poverty and psychosocial adversity.

## **2997 (3000 limit)**

### **Background**

Major depressive disorder (MDD) is a leading global cause of lifelong disability. The incidence markedly rises during mid-adolescence<sup>1-3</sup> and first onset at this age predicts a chronic long-term trajectory of symptoms into adult life<sup>4-6</sup> with especially poor long-term mental health, social and educational outcomes<sup>2,4-7</sup>. Even when the onset of depression is in adult life many of its contributing risk factors begin during childhood<sup>8-9</sup>, highlighting the importance of understanding the etiology of early-onset MDD<sup>10</sup>. The most common major risk factor for early-onset MDD is depression in a parent<sup>6,11-13</sup>. The adolescent offspring of depressed parents are therefore an important group for investigating the initial development of early-onset MDD.

MDD has a complex multi-factorial etiology that includes inherited/familial influences<sup>13-18</sup> and social risk factors<sup>8,9,19,20</sup>. How do such risks collectively impact on the child and eventually translate into first onset MDD? The childhood symptom dimensions of depression (low mood), anxiety/fear and conduct and oppositional problems have individually been found to precede later mood disorder<sup>21-24 25,26</sup>. Irritability may be a distinct dimension of oppositional behavior that independently predicts depressive symptomatology<sup>27-29</sup>. Familial/genetic and social risk factors may therefore increase the probability of incident MDD through earlier effects on these symptom dimensions which appear to be antecedents to disorder.

Despite a consensus that depression has multi-factorial causes and likely involves multiple risk pathways that begin in childhood, high-risk studies to date have documented elevated life-time rates of depressive disorder in those at familial risk but have not tested which developmental processes are involved in the initial onset of MDD in these individuals. This would be informative for refining primary prevention methods. Depression prevention efforts currently focus on modifying low mood, with particularly promising results when prevention is targeted at those at elevated risk for MDD including the offspring of depressed parents<sup>30-32</sup>. However, there are different developmental routes into first-onset MDD: if these

can be identified, targeting relevant risk factors and clinical antecedents could potentially be useful adjuncts to existing prevention programs<sup>33</sup>.

A focus on identifying processes involved in the first-onset of adolescent depression is warranted given the very high rates of recurrence when depression arises at this time<sup>4</sup>. This is the first paper to examine the antecedents of the *initial* onset of major depressive disorder during adolescence in a high-risk sample using an approach that models risk factors simultaneously and accounts for the co-occurrence of such risks. We set out to test whether multiple indicators of familial risk and social adversity simultaneously impact on first-onset MDD via anxiety, low mood, disruptive behavior and irritability in a high-risk longitudinal study of child and adolescent offspring of parent(s) with a history of recurrent major depressive disorder.

## **Methods**

### **Participants**

Data were from a prospective longitudinal study of the offspring of parents with recurrent depression. At baseline, there were 337 families (315 mothers and 22 fathers) recruited primarily from UK general practices<sup>34</sup>. The presence of least two episodes of DSM-IV major depressive disorder (MDD) in the index parent was confirmed at baseline with a timeline of the index parent's previous depressive episodes<sup>35,36</sup> and the SCAN (Schedules for Clinical Assessment in Neuropsychiatry)<sup>37</sup> assessed current parental depression. One child per family was included. The youngest child between 9 to 17 years was selected to reduce the likelihood that children had already experienced MDD (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to and living with the affected parent. Additional exclusion criteria were moderate-severe intellectual disability (IQ<50) in the child and DSM-IV criteria for bipolar disorder, mania/hypomania or psychotic disorder in the parent at interview. Two families were excluded as the index parent was subsequently diagnosed with bipolar disorder. Parents and offspring were assessed on three occasions. The average time between the baseline (T1) and second assessment (T2) was 16.2 months

and between the second and third (T3) assessment was 12.5 months. Data were collected via semi-structured diagnostic interviews and questionnaires<sup>38</sup>. Written informed consent or assent was obtained from parents and children as appropriate. The Multi-Center Research Ethics Committee for Wales approved the study.

### **Outcome variables at follow-up (T2 and T3)**

#### *Primary outcome: New-onset major depressive disorder (MDD) in offspring*

Child psychopathology was assessed with the Child and Adolescent Psychiatric Assessment (CAPA),<sup>39</sup> which is a semi-structured diagnostic interview that derives psychiatric symptoms and diagnoses over the preceding three months<sup>39,40</sup>. The parent and child assessments were completed independently by trained, supervised interviewers. A modified section of the CAPA was used to collect information on MDD symptoms occurring prior to the study and in between assessments. MDD was defined as the presence of at least 5 depressive symptoms including one of the core symptoms of low mood/irritability or loss of interest plus depression-related impairment (assessed with the incapacity section of the CAPA)<sup>41</sup>.

Diagnosed and sub-threshold cases were reviewed by two experienced child and adolescent psychiatrists. The primary outcome was new-onset offspring MDD defined as MDD at either T2 or T3 assessment. To increase confidence that we were identifying **first-onset** MDD cases, we excluded those with a diagnosis of MDD prior to T1 or at T1 (n=27), an episode that occurred but remitted between follow-up assessments (n=4) and those with missing MDD diagnostic information at baseline (n=2). This resulted in a maximum sample of 304 families. Diagnostic data at follow-up were available for 279 individuals (92%).

#### *Secondary outcome: Major depressive disorder (MDD) symptoms in offspring*

A total of all DSM-IV MDD symptoms defined by the CAPA at follow-up (an average of the total symptoms aggregated across T2 and T3) was calculated.



## **Predictor variables assessed at baseline (T1)**

### *Dimensional clinical antecedents*

#### *Low mood symptoms*

The Mood and Feelings Questionnaire (MFQ) is a widely accepted depression screening instrument and was used to generate a full range of low mood scores<sup>42</sup>. It includes 34 items about the child's mood symptoms over the past three months rated from 0 (not true) to 2 (true)<sup>43</sup>. Scores across informants were combined by using the highest rating per item from either the parent or the child. Internal reliability was excellent ( $\alpha = .95$ ). We did not use the CAPA depression score as a predictor to avoid the possibility of criterion contamination when predicting new-onset MDD at follow-up diagnosed using the CAPA and because the threshold for endorsing an MDD symptom is very high<sup>41</sup>.

#### *Anxiety/fear*

The Screen for Child Anxiety and Related Emotional Disorders (SCARED) is a 41-item questionnaire<sup>44,45</sup> that assesses children's symptoms of anxiety (generalized, panic, somatic, school, separation and social anxiety) rated from 0 (not true/hardly ever true) to 2 (very true/often true)<sup>45,46</sup>. Internal reliability was excellent ( $\alpha = .93$ ). Parent and child data were combined as above for low mood.

#### *Disruptive behavior and irritability*

Symptoms of oppositional defiant disorder were assessed with the CAPA. Irritability scores were calculated by combining the items (0 absent; 1 present): 'touchy or easily annoyed', 'angry or resentful' and 'temper tantrums'<sup>47,48</sup>. The items 'disobedient/break rules', 'annoys others', 'blames others' and 'spiteful or vindictive' created a disruptive behavior score. Both scales showed adequate internal consistency ( $\alpha = .61$ ;  $\alpha = .61$ ).

### *Indices of degree of familial risk*

Severity of parental MDD<sup>16,34</sup> and familial loading for MDD in additional family members<sup>17</sup> indexed the degree of offspring familial risk. Using a life history calendar<sup>35,36</sup> parents reported on any hospitalizations for depression and gave details of their previous worst two episodes of depression and associated impairment<sup>49</sup>. A severe episode of depression was defined as a period of hospitalization due to depression or an episode of depression with severe impairment in at least one area of functioning (GAF score  $\leq 50$ )<sup>38,49</sup>. Family history of depression additional to the index parent was ascertained by asking parents about a diagnosis of depression in first- and second-degree relatives of the child. The number of family members with a history of depression was weighted by relatedness<sup>17</sup>.

### *Social adversity indices*

A measure of recent psychosocial adversity was derived from recent stressful life events<sup>50</sup>. A total score was calculated by summing stressful events (possible  $n=21$ ) occurring within the past 12 months. Sample items include: 'death of a close friend', 'serious illness', 'being bullied', 'increased quarrelling between parents'. Where a life event was reported by the parent or the child, it was considered present<sup>51</sup>.

Low parent-reported household income was considered as a measure of economic disadvantage and defined as gross household income  $\leq$  £20,000<sup>52</sup> which in this sample is equivalent to the international definition of poverty ( $<60\%$  of median income)<sup>53</sup>.

## **Statistical analysis**

Structural equation modelling (SEM), which enables simultaneous assessment of all hypothesized risk paths was carried out. Figure 1 shows the full estimated model, and

results are presented as standardized beta coefficients. We hypothesized that low mood, fear/anxiety, irritability and disruptive behavior would each independently behave as antecedents, even allowing for correlations between them, given previous evidence for each as a clinical antecedent of MDD<sup>21,23,24,26,48</sup>. Furthermore it was hypothesized that indicators of familial (parental depression severity, additional family history of depression) and social risk (recent psychosocial adversity, economic disadvantage) would have both direct and indirect effects (via the clinical antecedents) on new-onset MDD. Analyses were conducted using LISREL<sup>54</sup>. A polyserial covariance matrix was estimated in PRELIS prior to analyses as some variables were binary. 304 cases were available. Little's test indicated that data were missing completely at random ( $\chi^2 (18) = 16.13, p = .583$ ). Full Information Maximum Likelihood estimation enabled use of all available data. Fit of the final model was excellent ( $\chi^2 (10) = 7.75, p = .653$ ; RMSEA = .00 (.00, .05); CFI = 1.00; SRMR = .01). Indirect effects were estimated controlling for the effect of the paths from other risk factors to the clinical antecedents. Analysis was conducted between September 1 2015-to May 27 2016 and revisions between 10 August-20<sup>th</sup> September, 2016.

## Results

Descriptive statistics are shown in Table 1. On average, individuals had 1.85 DSM-IV symptoms of MDD at follow-up (range= 0-8; standard deviation = 1.74). 20 individuals had *new-onset* MDD during the study (6 male, 14 female; average age at onset =14.4 years, range 10-18).

<TABLE 1 HERE>

The results of SEM analyses for the primary outcome of new-onset MDD are shown in Figure 1 and described below.

<FIGURE 1 HERE>

#### *Dimensional clinical antecedents*

Irritability was associated with new-onset MDD ( $\beta = .12, p < .05$ ), as was fear/anxiety ( $\beta = .38, p < .01$ ). In contrast, allowing for other effects in the full model, disruptive behavior was not associated with new-onset MDD ( $\beta = -.08, p > .1$ ), nor was low mood ( $\beta = -.03, p > .1$ ). To compare the magnitude of the two paths showing significant association with new-onset MDD (irritability and fear/anxiety) we constrained them to be equal which resulted in a significant  $\chi^2$  change ( $\chi^2 (1) = 9.09, p = .003$ ) indicating that the path from fear/anxiety to new-onset MDD was significantly stronger than the path for irritability. The correlation between fear/anxiety and irritability was low but significant (Figure 1;  $\beta = .14, p < .05$ ) suggesting they do not frequently co-occur.

#### *Indices of familial risk*

The direct paths from additional family history of depression to new-onset MDD ( $\beta = .10, p < .05$ ) and from parent depression severity to new-onset MDD ( $\beta = .24, p < .01$ ), were significant. Neither of the indices of familial risk were associated with any clinical antecedent.

#### *Indices of social risk*

Both economic disadvantage and recent psychosocial adversity had significant direct effects on new-onset MDD ( $\beta = .12, p < .05$ ;  $\beta = .22, p < .01$ , respectively). In addition, economic disadvantage and recent psychosocial adversity were associated with all the clinical antecedents.

#### *Indirect effects*

We hypothesised that indices of familial and social risk would influence risk for new-onset MDD indirectly via the dimensional clinical antecedents as well as directly. None of the indirect effects was significant: economic disadvantage to new-onset MDD via irritability ( $\beta = .007, p > .1$ ); economic disadvantage to new-onset MDD via fear/anxiety ( $\beta = -.012, p > .1$ ) recent psychosocial adversity via fear/anxiety ( $\beta = -.012, p > .1$ ) and irritability ( $\beta = .003, p > .1$ ).

## Secondary analyses

CAPA-derived DSM-IV MDD symptoms were assessed as a secondary outcome (see supplementary table 1). The pattern of results was extremely similar to those for the primary outcome. The only exception was that the paths to MDD symptoms from irritability and from fear/anxiety were not significantly different ( $\chi^2 (1) = 0.27, p = .605$ ). The small number of affected boys (Table 1) precluded examination of gender differences for new-onset MDD. We also thought it important to examine age effects by excluding any pre-pubertal onset MDD cases (< 10 years) given evidence these may differ from pubertal-onset cases<sup>22</sup> and cases where irritability was the defining MDD mood symptom. However, there were no such cases. Additional sensitivity analyses (supplementary section) examined which of the separate aspects of fear/anxiety (e.g. generalized anxiety, social anxiety etc) was most associated with new-onset MDD and results suggested that generalized anxiety symptoms were driving the predictive effect of fear/anxiety on new-onset MDD.

## Discussion

In a longitudinal high-risk study of MDD we examined mechanisms underlying the development of first episode of adolescent-onset MDD in those at high familial-risk. Simultaneous testing of different pathways suggested six routes into adolescent-depression (two via clinical antecedents and four via familial/genetic and social risk factors). Both fear/anxiety and irritability predicted new adolescent-onset MDD and MDD symptom count. These effects were independent of each other as well as of low mood and disruptive behavior. These antecedents are often examined individually and are correlated with each other; to our knowledge, their joint contribution has not been examined together in this way. The observation that irritability and not other aspects of oppositional behavior increased risk for new-onset MDD is consistent with results from population-based studies<sup>48,55,23,26</sup>. Sub-threshold low mood symptoms are known to predate depression<sup>21,24</sup>. Thus, the finding that

fear/anxiety predicted new-onset MDD over and above the effect of low mood may seem surprising but these dimensions are highly correlated (Figure 1). Whilst, anxiety and depression cross predict each other over time,<sup>26,56-62</sup> anxiety typically emerges earlier<sup>22</sup> which may contribute to the stronger predictive effect observed for fear/anxiety on first adolescent-onset MDD. Sensitivity analyses illustrated that generalized anxiety symptoms were driving the predictive effect of fear/anxiety on new-onset MDD. Overall, our findings suggest that considering additionally targeting anxiety and/or irritability<sup>63,64</sup> in the child seems warranted. Investigating the neural/behavioral correlates of fear/anxiety and irritability may help elucidate *how* these dimensions increase MDD risk<sup>65</sup>.

We predicted that indicators of familial loading and social risk would influence risk for MDD indirectly via effects on dimensional clinical antecedents. We did not find evidence for this and all the indirect paths were non-significant. In contrast, there were significant direct effects of all familial/genetic and social risk factors on MDD. The indicators of familial and social risk thus predicted MDD independently of correlated familial risk, parental depression severity and clinical antecedents in the child. This has important implications for treatment and prevention and highlights the need to not only resolve clinical phenomena in the child but also wider contextual difficulties. Effective prevention of adolescent MDD is important given the potential for long-term beneficial effects on adult functioning<sup>66</sup>. Our findings suggest that primary prevention methods for depression in high-familial-risk groups will not only need to include effective treatment of parental depression<sup>30,67,68</sup>, anxiety and irritability in the child, but will also need to consider social risk factors. Family-based programs may be indicated in youth at high familial-risk of depression because parental depression is associated with social adversity (poverty and stress-exposure)<sup>69-71</sup> and moderates the effectiveness of preventive programs focusing on the child<sup>30,72</sup>. Our findings underscore the potent impact of social risks in the initial development of adolescent depression<sup>52,69,73,74</sup>.

Whilst this study has a number of important strengths including the use of a large, prospective longitudinal high-risk study with repeated measurement using comprehensive psychiatric assessments allowing a novel focus on incident cases of new-onset MDD, low

rates of attrition across assessments, and use of a method appropriate for simultaneously modelling multiple correlated risk effects, results should be interpreted bearing in mind a number of considerations and limitations. First, although the rates of MDD were higher than comparable community studies<sup>59</sup>, participants in this sample have not yet gone through the peak period of risk for MDD which occurs in early adult life and thus the numbers with MDD are relatively low. However, results replicated for MDD symptom count. Second, we selected clinical antecedents and indicators of familial and psychosocial risk on the basis of empirical evidence<sup>6,8,9,17,20,21,23,26,27,48</sup>. However, it is inevitable that some variables viewed to be important because they are disrupted in major depression (e.g. parenting<sup>75</sup>, neuropsychological/cognitive dysfunction<sup>76</sup>) will have been omitted. Measurement differences between constructs may also contribute to results, for instance, the clinical antecedent construct of fear/anxiety contained more items than that for irritability. Third, we cannot rule out person effects on the environment i.e. that individuals to some extent 'elicit' environmental risk exposure through their behavior<sup>77,78</sup>. However, it seems unlikely that children 'elicit' economic adversity and evidence suggests causal effects of psychosocial adversity on MDD when accounting for inherited influences on environmental exposure<sup>79</sup>. Fourth, as would be expected, there were a relatively small number of males with MDD in the sample meaning that we were unable to assess gender differences in the pathways to first-onset MDD. Gender differences in the pathways to life-time adult-onset MDD have been reported<sup>80-82</sup> and thus whether there are gender differences in the pathways to the incidence of adolescent-onset MDD will require future investigation. Joint analyses across multiple data sets may be needed which could also incorporate the gender of the parent. Fifth, we assessed indicators of familial-risk for MDD using data from clinical interview as opposed to measured genotypes. However, family-history provides complementary information to molecular genetic risk-scores<sup>83</sup>. Sixth, the sample consisted overwhelmingly of depressed mothers making it unclear to what extent findings would generalize to the offspring of depressed fathers.

This study of children and adolescents at high familial-risk of MDD shows that fear/anxiety and irritability are important clinical antecedents of new-onset MDD but that familial and social risk factors additionally contribute to risk for the initial onset of adolescent MDD. Primary prevention/early intervention strategies may need to target, not only clinical features in the high-risk child and the parent, but also incorporate public health and community strategies to help overcome social risks most notably poverty and psychosocial adversity.



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## Figure Legends

**Figure 1. Structural equation model examining pathways to new-onset Major Depressive Disorder (MDD).** F.H: Family history; \*  $p < .05$ ; \*\*  $p < .01$ ; † paths significantly differ. Dashed paths are not statistically significant.

## Tables

*Table 1: Descriptive statistics*

Construct	Mean, SD (range) or percentage (n)
<b>Indicators of social and genetic risk (baseline)</b>	
Additional family history <sup>a</sup>	0.75, 0.86 (0-6)
Parent severe depression <sup>b</sup>	68% (205/303)
Parent GAF score (worst episode)	42.46, 17.45 (4-90)
Economic disadvantage <sup>c</sup>	28.6% (80/280)
Recent psychosocial adversity <sup>d</sup>	3.30, 2.30 (0-12)
<b>Dimensional clinical antecedents (baseline)</b>	
Irritability	1.33, 1.12 (0-3)
Disruptive behavior	1.51, 1.79 (0-8)
Fear/anxiety	23.49, 14.82 (0-63)
Low mood	18.46, 13.18 (0-62)
<b>Primary and secondary outcomes (follow-up)</b>	
New-onset MDD	7% (20/279) (14 Females; 6 Males)
Age of onset	14.4, 2.33 (10, 18)
Depressive symptoms	1.85, 1.74 (0-8.5)

<sup>a</sup> Number of first and second degree relatives with depression weighted by relatedness

<sup>b</sup> GAF score <50 or hospitalization for depression

<sup>c</sup> Gross family income: proportion <£20,000

<sup>d</sup> Number of recent stressful life events